

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: BARRY L. DAVISON
DAVIS WRIGHT TREMAINE LLP
2600 CENTURY SQUARE
1501 FOURTH AVENUE
SEATTLE, WA 98101-1688

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

RECEIVED
AUG 27 2001
DWT PATENT DEPT

Applicant's or agent's file reference 47675-19	Date of Mailing (day/month/year) 24 AUG 2001
International application No. PCT/US01/10658	FOR FURTHER ACTION See paragraphs 1 and 4 below International filing date (day/month/year) 02 APRIL 2001
Applicant UNIVERSITY OF CALIFORNIA	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.
- Filing of amendments and statement under Article 19:**
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):
- When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.
- Where?** Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35
- For more detailed instructions, see the notes on the accompanying sheet.
2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
4. **Further action(s):** The applicant is reminded of the following:
- Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.
- Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).
- Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
LISA ARTHUR

Telephone No. (703) 308-3988

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 47675-19	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US01/10658	International filing date (day/month/year) 02 APRIL 2001	(Earliest) Priority Date (day/month/year) 31 MARCH 2000
Applicant UNIVERSITY OF CALIFORNIA		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

i. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No. _____
- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.
- ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/10658

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68

US CL : 435/6

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6: 536/24.31, 24.33

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	KAWAKAMI, K et al. Hypermethylated APC DNA in plasma and prognosis of patients with esophageal adenocarcinoma. Journal of the National Cancer Institute. 15 November 2000. vol. 92., No. 22, pages 1805-1811, see entire document.	1-24
Y,P	EADS, C.A. et al. Fields of Aberrant CpG Island Hypermethylation in Barrett's Esophagus and associated Adenocarcinoma. Cancer Research. 15 September 2000. Vol. 50, pages 5021-5026, see entire document.	1-24
Y	SUZUKI, H. et al. Intragenic mutations of CDKN2B and CDKN2A iHn Primary human esophageal cancers. Human Molecular Genetics. 1995. Vol. 4. no. 10, pages 1883-1887, see entire document.	1-24



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"g" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

24 JULY 2001

Date of mailing of the international search report

24 AUG 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

LISA ARTHUR

Telephone No. (703) 308-3988

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CODY, D.T, ii et al. Differential DNA methylation of the p16 INK4A/CDKN2A promoter in human oral cancer cells and normal human oral keratinocytes. ORAL ONCOLOGY. 1999, Vol. 35, pages 516-522, see entire document.	1-10, 13, 15-24
Y	GRAFF, J.R. et al. Distinct patterns of E-Cadherin CpG island methylation in papillary, follicular, Hurtle's cell and poorly differentiated thyroid carcinoma. Cancer Research. 15 May 1998, Vol. 58, pages 2063-2066, see entire document.	1-10, 15-24
Y	IWASE, H. et al. DNA methylation analysis at distal and proximal promoter regions of the oestrogen receptor gene in breast cancers. British Journal of Cancer. 1999, Vol. 80. No. 12, pages 1982-1986, see entire document.	1-10, 15-24
Y	MILLAR, D. S. et al. Detailed methylation analysis of the glutathione S-transferase(GSTP1) gene in prostate cancer. ONCOGENE. 1999, Vol. 18. pages 1313-1324, see entire document.	1-10, 15-24
Y	JHAVERI, M.S. et al. Methylation-mediated regulation of the glutathione S-transferase Pi gene in human breast cancer cells. Gene (1998) Vol. 210, pages 1-7, see entire document.	1-10 and 15-24
Y	BARRETT, M.T. et al. Evolution of neoplastic cell lineages in Barrett oesophagus. Nature Genetics. May 1999, Vol. 22. pages 106-109, see entire document.	1-24
Y	HERMAN, J.G. et al. Incidence and functional consequences of hMLH1 promoter hypermethylation in colorectal carcinoma. Proceedings of the National Academy of Sciences. June 1998. vol. 95. pages 6870-6875, see entire document.	1-11, 13, 15-24
Y	ESTELLER, M et al. Inactivation of the DNA Repair gene O6-methylguanine-DNA methyltransferase by promoter hypermethylation is a common event in primary human neoplasia. Cancer Research, 15 February 1999. Vol. 59. pages 793-797, see entire document.	1-24
Y	IACOPETTA, B.J. et al. Hypermethylation of the Myf-3 gene in human colorectal cancer. Anticancer Research. 1997. Vol. 17. pages 429-432, see entire document.	1-11, 13, 15-24
Y	ESTELLER, M. et al. Hypermethylation-associated inactivation of p14ARF is independent of p16INK4A methylation and p53 mutational status. Cancer Research. 01 January 2000. Vol. 60, pages 128-133, see entire document.	1-24

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/10658

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y,P	NAKAMURA, M. et al. Promoter hypermethylation of the RB1 gene in glioblastomas. Laboratory Investigations. January 2001. Vol. 81. no. 1, page 77-82, see entire document.	1-10, 15-24
Y	MEKI, J.R. et al. Cancer-specific region of hypermethylation identified within the HIC1 putative tumour suppressor gene in acute myeloid leukaemia. Leukemia. 1999. Vol. 13. pages 877-883, see entire document.	1-10, 15-24

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

WEST, MEDLINE, BIOSIS, EMBASE, CAPLUS

search terms: hypermethylation, cpg islands, apc, arf, calca, cdh1, cdkn2a, cdkn2b, esr1, gstp1, hic1, mgmt, mlh1, myd1,
rb1, tgbt2, thbs1, timp3, cttnb1m ptgs2, tyns, mthfr